Antimicrobial Prescribing and Stewardship

John Ferguson, Microbiology & Infectious Diseases, John Hunter Hospital, University of Newcastle, NSW, Australia

M Med Part 1 updates

UPNG 2019

Tw @mdjkf   http://idmic.net
Antibiotic usage drives resistance!
Correlation of resistance with Antimicrobial Use in Community-Acquired Infections in Europe, 1997-2000

Each dot represents a different European nation

A very tight relationship between overall community consumption and resistance (erythromycin is a macrolide)

How are antibiotics used in PNG?

• PMGH (Steven Yennie, 2012)
  – Medical ward 72% of patients receiving an anti-infective (excluding TB and ARV treatment)

• Alotau Hospital (Nick Ferguson, Nov 2012)
  – Medical ward: 60% of patients on anti-infective
  – Obstetric ward: 34%

**Common survey findings**

• Very prolonged courses, prolonged IV courses
• Undocumented reasons for therapy
• Treatments not in accord with Standard Treatment Guidelines
Insufficient numbers of Gram negative isolates to produce antiibiogram; 
Pseudomonas aeruginosa – 24 isolates; gentamicin 54% susceptible, cipro 63%
# Urines – species > 30 isolates

## PMGH 2016 Urine antibiogram

<table>
<thead>
<tr>
<th>Species</th>
<th>Isolates</th>
<th>Ampicillin</th>
<th>Ampicillin + clavulanate</th>
<th>Cefazolin / cephalaxin</th>
<th>Nitrofurantoin</th>
<th>Trimethoprim + sulfamethoxazole</th>
<th>Gentamicin (aminoglycoside)</th>
<th>Ceftriaxone</th>
<th>Norfloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>52</td>
<td>8%</td>
<td>17%</td>
<td>n/a</td>
<td>96%</td>
<td>26%</td>
<td>79%</td>
<td>83%</td>
<td>79%</td>
</tr>
<tr>
<td><em>Klebsiella species</em></td>
<td>31</td>
<td>R</td>
<td>23%</td>
<td>n/a</td>
<td>50%</td>
<td>26%</td>
<td>47%</td>
<td>38%</td>
<td>78%</td>
</tr>
</tbody>
</table>

**n/a** Not available - not routinely tested in this laboratory or no testing standard available

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>93%</td>
<td>&gt; 90% of isolates susceptible</td>
</tr>
<tr>
<td>75%</td>
<td>Susceptible by extrapolation or intrinsically susceptible</td>
</tr>
<tr>
<td>45%</td>
<td>&lt; 70% of isolates susceptible</td>
</tr>
<tr>
<td>R</td>
<td>Intrinsically resistant</td>
</tr>
</tbody>
</table>
PNG therapeutic resources

Adult Medicine
- Adult medical standard treatment guide- 2012.
- HIV Adult standard treatment guideline 2009 March. This is the current version in use in 2012.

Paediatrics
- PNG Paediatric standard treatment guides Main resource site
- WHO Integrated Management of Childhood Illness resources
- Recommendations for management of common childhood conditions 2012. Excellent evidence-based extensive review.
- International Child Health Review Collaboration
- Royal Childrens Hospital Melbourne Paediatric Handbook 8th Edition
- WHO Treatment of Children living with HIV
- Manual on paediatric HIV care and treatment for district hospitals WHO 2011

Obstetrics and Gynaecology

Surgery
- Standard Treatment book - awaited
- WHO Guidelines for Safer Surgery 2009

See also Safer surgery: resource poor countries

PNG Medical Journal
Full index to all issues with text links are available from here. The PNGMJ is indexed by Medline and so the easiest way to search.
See this quick start guide to PUBMED for more instructions. It is essential for practitioners in PNG to be aware of the local literature in PNG which have been well researched in the past.

http://idmic.net
Q1. What is the primary aim(s) of antimicrobial stewardship?

- Reduce antibiotic resistance generally by reducing antibiotic selective pressure on bacteria
- Improve the effectiveness of antibiotic treatment of individual patients with infection
- Improve patient safety by reducing unintended consequences of antibiotic treatment

<table>
<thead>
<tr>
<th>Correct response</th>
<th>Results (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All three is the correct answer</td>
<td>90%</td>
</tr>
</tbody>
</table>
Purpose of antimicrobial stewardship

1. Optimise outcome for patient with infection - right diagnosis, right antibiotic, timing, dose, duration etc

2. Reduce antimicrobial resistance

3. Minimise individual and community unintended consequences of antimicrobials - adverse events, added (super)infection
## Unintended consequence: antibiotic mortality

<table>
<thead>
<tr>
<th>Antibiotic class</th>
<th>Mechanism</th>
<th>Mortality risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td>Aplastic anaemia</td>
<td>1 in 20-60,000 courses</td>
</tr>
<tr>
<td>Betalactams</td>
<td>Anaphylaxis</td>
<td>1 in 50-66,000 courses</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Hyperkalaemia from reduced distal renal tubular tubular K secretion</td>
<td>In a population of patients &gt; 65 years on ACE inhibitors, excess mortality of 1 in 350 courses</td>
</tr>
<tr>
<td>Macrolides (azithromycin)</td>
<td>Prolonged QT – sudden death</td>
<td>1 in 26,000 courses (33 studies involving 20,779,963 participants)</td>
</tr>
<tr>
<td>Quinolones (ciprofloxacin and others)</td>
<td>Prolonged QT – sudden death</td>
<td>Similar level of risk for ciprofloxacin death in the trimethoprim study above Risk remains higher for 2 weeks following rx</td>
</tr>
</tbody>
</table>
Clinicians as stewards

“Stewardship is an ethic that embodies the responsible planning and management of [scarce] resources.” Wikipedia

Leadership, advocacy and collaboration amongst prescribers required to reduce AMR.

We have the agency and scope to change patient management in ways that will reduce the impact of AMR on our patients and the community
Start Smart, Then Focus
An Antibiotic Care Bundle for Hospitals

Day 1: Start Smart...

1. Start antibiotics **only** if there is clinical evidence of bacterial infection
   - If there is evidence of bacterial infection, prescribe in accordance with your local antibiotic guidelines and appropriately for the individual patient (see notes below)

2. Obtain appropriate cultures before starting antibiotics

3. Document in both the drug chart and medical notes:
   - Treatment indication
   - Drug name, dose, frequency and route
   - Treatment duration (or review date)

4. Ensure antibiotics are given within four hours of prescription
   - Within 1 hour for severe sepsis or neutropenic sepsis

When deciding on the most appropriate antibiotic(s) to prescribe, consider the following factors:
- History of drug allergy (document allergy type: minor (rash only) or major (anaphylaxis, angioedema))
- Recent culture results (e.g. is patient colonised with a multiple-resistant bacteria?)
- Recent antibiotic treatment
- Potential drug interactions
- Potential adverse effects (e.g. *C. difficile* infection is more likely with broad spectrum antibiotics)
- Some antibiotics are considered unsafe in pregnancy or young children
- Dose adjustment may be required for renal or hepatic failure

Consider removal of any foreign body/indwelling device, drainage of pus, or other surgical intervention

...then Focus (Day 2 onwards)

At 24-48 hours after starting antibiotics, make an **Antimicrobial Prescribing Decision**
- Review the clinical diagnosis
- Review laboratory/radiology results
- Choose one of the five options below
- Document this decision

**Options**

1. Stop antibiotic(s)
   - no evidence of bacterial infection, or infection resolved

2. Switch from intravenous to oral antibiotic(s)
   - if patient meets criteria for oral switch

3. Change antibiotic(s)
   - narrower spectrum, if possible; broader spectrum, if indicated

4. Continue current antibiotic(s)
   - review again after further 24 hours

5. Outpatient parenteral antibiotic therapy
   - consult with local OPAT team
UK: country-wide experiment – restrictions on cephalosporin and quinolone use implemented

Declining usage: hospital antibiotic sales (kg), IMS data

Slides courtesy of Neil Woodford, HPA 2012
AMR is dynamic - reducing use will usually reduce resistance

E. coli from blood & CSF in the UK - a recent fall in resistance

- coincides with decreased use = decreasing selection?
- If plasmids can’t be lost, is this strain displacement?
John Hunter Hospital (NSW): MRSA and VRE acquisitions and infections fell promptly when piperacillin/tazobactam usage was replaced with lesser spectrum agent (augmentin)
Q2: What class of antibiotic is vancomycin?

1. Betalactam
2. Aminoglycoside
3. Glycopeptide
4. Tetracycline
5. Not sure
Q2: What class of antibiotic is vancomycin?

<table>
<thead>
<tr>
<th>Correct response</th>
<th>Results (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycopeptide</td>
<td>17%</td>
</tr>
</tbody>
</table>

- Why understand the class? Differences in:
  - Pharmacodynamics and dosing
  - Toxicity potential
  - Antibacterial spectrum
  - Mechanisms of resistance
DIFFERENT CLASSES OF ANTIBIOTICS - AN OVERVIEW

**Key:**
- **COMMONLY ACT AS BACTERIOSTATIC AGENTS, RESTRICTING GROWTH & REPRODUCTION**
- **COMMONLY ACT AS BACTERICIDAL AGENTS, CAUSING BACTERIAL CELL DEATH**

**6-LACTAMS**
- **MOST WIDELY USED ANTIBIOTICS IN THE NHS**
- **ALL CONTAIN A β-LACTAM RING**
  - **EXAMPLES**
    - Penicillins (shown), such as amoxicillin and flucloxacillin
    - Cephalosporins such as cefalexin
- **MODE OF ACTION**
  - Inhibit bacterial cell wall biosynthesis.

**AMINOGLYCOSIDES**
- **FAMILY OF OVER 20 ANTIBIOTICS**
- **ALL CONTAIN AMINOGLYCOSIDE SUBSTRUCTURES**
  - **EXAMPLES**
    - Streptomycin (shown), neomycin, kanamycin, paromomycin
- **MODE OF ACTION**
  - Inhibit the synthesis of proteins by bacteria, leading to cell death.

**CHLORAMPHENICOL**
- **COMMONLY USED IN LOW INCOME COUNTRIES**
- **DISTINCT INDIVIDUAL COMPOUND**
  - **EXAMPLES**
    - Chloramphenicol, clindamycin
- **MODE OF ACTION**
  - Inhibit the synthesis of proteins by bacteria, preventing growth.

**GLYCOPEPTIDES**
- **COMMON DRUGS OF LAST RESORT**
- **CONSIST OF CARBOHYDRATE LINKED TO A PEPTIDE FORMED OF AMINO ACIDS**
  - **EXAMPLES**
    - Vancomycin (shown), teicoplanin
- **MODE OF ACTION**
  - Inhibit bacteria cell wall biosynthesis.

**QUINOLONES**
- **RESISTANCE EVOLVES RAPIDLY**
- **ALL CONTAIN FUSED CYCLOPROPANE RINGS WITH A CARBONYL ACID GROUP ATTACHED**
  - **EXAMPLES**
    - Ciprofloxacin (shown), levofloxacin, trovafloxacin
- **MODE OF ACTION**
  - Interfere with bacteria DNA replication and transcription.

**OXAZOLIDINONES**
- **POTENT ANTIBIOTICS COMMONLY USED AS ‘DRUGS OF LAST RESORT’**
- **ALL CONTAIN 2-EXOXYNEON CARBONATE IN THEIR STRUCTURE**
  - **EXAMPLES**
    - Linezolid (shown), tazobactam, ocrexin, cipenem
- **MODE OF ACTION**
  - Inhibit synthesis of proteins by bacteria, preventing growth.

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**DISCOVERY**
- **1930**
- **1940**
- **1950**
- **1960**
- **1970**
- **1980**

**SULFONAMIDES**
- **FIRST COMMERCIAL ANTIBIOTICS WERE SULFONAMIDES**
- **ALL CONTAIN THE SULFONAMIDE GROUP**
  - **EXAMPLES**
    - Prontosil, sulфamethizide, sulfasalazine
- **MODE OF ACTION**
  - Do not kill bacteria but prevent their growth and multiplication. Cause allergic reactions in some patients.

**TETRACYCLINES**
- **BECOMING LESS POPULAR DUE TO DEVELOPMENT OF RESISTANCE**
- **ALL CONTAIN 4-ADJACENT CYCLIC HYDROCARBON RINGS**
  - **EXAMPLES**
    - Tetracycline (shown), doxycycline, minocycline, oxytetracycline
- **MODE OF ACTION**
  - Inhibit synthesis of proteins by bacteria, preventing growth.

**MACROLIDES**
- **SECOND MOST PRESCRIBED ANTIBIOTICS IN THE NHS**
- **ALL CONTAIN A 14-, 15-, OR 16-MEMBERED MACROCYCLE**
  - **EXAMPLES**
    - Erythromycin (shown), clarithromycin, azithromycin
- **MODE OF ACTION**
  - Inhibit protein synthesis by bacteria, leading to cell death.

**ANSAMYCINS**
- **CAN ALSO DEMONSTRATE ANTIVIRAL ACTIVITY**
- **ALL CONTAIN AN AROMATIC RING BRIDGED BY AN ALIPHATIC CHAIN**
  - **EXAMPLES**
    - Garamycin (shown), rifabutin, rifampin, clarithromycin
- **MODE OF ACTION**
  - Inhibit the synthesis of RNA by bacteria, leading to cell death.

**STREPTOGRAMINS**
- **TWO GROUPS OF ANTIBIOTICS THAT ACT SYNERGETICALLY**
- **ALL CONTAIN A LIPID BONDED TO A PEPTIDE**
  - **EXAMPLES**
    - Daptomycin (shown), suramycin
- **MODE OF ACTION**
  - Disrupt multiple cell membrane function, leading to cell death.

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[https://aimed.net.au/2017/02/01/antibiotic-classes-why-so-important-to-know-about-them/](https://aimed.net.au/2017/02/01/antibiotic-classes-why-so-important-to-know-about-them/)
PK and PD

• **Pharmacokinetics** describes the time course of drug levels in body fluids as a result of absorption, distribution, and elimination of a drug after administration. Parameters include:
  – Bioavailability and influence of food on absorption
  – Peak level
  – Vd- Volume of distribution (lipo versus hydrophilic drugs)
  – T1/2 - Half life
  – AUC – area under the concentration-time curve

• **Pharmacodynamics** describes the rate and extent of bactericidal action and postantibiotic effects – used to provide a rational basis for determination of optimal dosing regimens in terms of the dose and the dosing interval

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3675903/
Maximising therapeutic effect

Dose in accord with PK/PD understanding:

1. **Time-dependent kill** – betalactams, vancomycin – ensure drug concentration above organism MIC for > 50% of the time; i.e. more frequent dosing gives better efficacy than higher doses

2. **Concentration-dependent kill** – aminoglycosides, quinolones, metronidazole - ensure drug dose high enough to achieve adequate kill – target area under the curve – AUC/MIC parameter used. Concentration dependent Post antibiotic effect (PAE)

3. **Bacteriostatic agents** that produce moderate to prolonged PAEs (e.g., macrolides, clindamycin, tetracyclines). Because of their prolonged PAE, their efficacy is determined less by time and more by the AUC that is greater than the MIC.
Therapeutic factors promoting antibiotic resistance

1. Antibiotic selective pressure
   - Number of patients exposed (volume of use)
   - Breadth of spectrum
   - Duration of use

2. Inadequate dosing
Eliminate unnecessary use

• Patients may receive antibiotics for extended post operative prophylaxis or for ‘just in case’ situations where there is little actual evidence of infection

• These exposures put patients at great risk of acquiring resistant organisms and should be avoided

(Post operative prophylaxis doesn’t protect patients from poor hygiene or hospital acquired infection)

Unnecessary use – trusting in scalpel-mycin

• Appendectomy
  – Post operative dosing largely unnecessary for unperforated cases; 4 days for others

• Cholecystectomy – cease antibiotics post op

• Diverticular disease
  – Antibiotics unnecessary for non-surgical patients (2 RCTs)

• Perforated viscus with source control achieved: 4 days (or less) sufficient; 2015 NEJM trial

Rational empirical antibiotic use

• Evaluate likelihood of sepsis by presence of SIRS, other organ system dysfunction
• Withhold antibiotics if there is not a strong case and severe sepsis is absent
• Do pre-antibiotic microbiology tests
• Select empirical antibiotic(s) based on local guidelines and AMR incidence
• Document the reason for antibiotics in the patient record

Start Smart
Narrow spectrum empirical treatment

- Skin/soft tissue infection without sepsis: surgical management; MRSA cover
- Community acquired pneumonia
- Early (< 5 days from admission) Hospital acquired pneumonia
Post empiric evaluation at 48-72 hours

Assess:

- Response to treatment
- Source control
- WCC, biochem and microbiology results – can treatment be directed against proven pathogen(s)?
- Is there a non-infective cause?
- Is antibiotic treatment still indicated (patient has rapidly improved)?
- If ongoing treatment indicated – consider early switch to oral (most agents are bioavailable)
- Define duration of treatment required

Then focus!
Limit durations of treatment

A very effective way to reduce selective pressure!

Shorter duration treatments are feasible with:

- community pneumonia (3-5d) - extensive studies
- Intensive care unit pneumonia (7d)
- Localised UTI (3 days), UTI with sepsis (7-10d)
- Intra-abdominal sepsis with source controlled (1-4d)

Local guidelines need to specify recommended durations

Paterson-D et al. Strategies for Reduction in Duration of Antibiotic Use in Hospitalized Patients Clinical Infectious Diseases 2011: 52: 1232
Limiting durations of treatment

Effective way to reduce selective pressure

Few situations require prolonged treatment:
- Endocarditis
- Prosthetic infections etc

Short, sharp and directed best idea
Single dose surgical prophylaxis!

Paterson-D et al. *Strategies for Reduction in Duration of Antibiotic Use in Hospitalized Patients* Clinical Infectious Diseases 2011: 52: 1232

Randomized clinical trial to compare a single dose with 3 doses of prophylactic antibiotic in open reduction and internal fixation of the fractures of long bones

IKAU KEVAU¹ AND JERZY KUZMA²

School of Medicine and Health Sciences, University of Papua New Guinea, Port Moresby and Faculty of Medicine and Health Sciences, Divine Word University and Modilon General Hospital, Madang, Papua New Guinea

SUMMARY

To reduce the incidence of surgical site infection (SSI), perioperative antimicrobial prophylaxis has long been advocated for joint replacement and open reduction with internal fixation of long bones. Increasing health care costs have focused hospital interest on more cost-effective procedures. Although current literature indicates that single-dose antibiotic prophylaxis is comparable to a 3-dose regimen, there are no reports from low-income countries. The primary aim of this study was to compare the infection rate following open reduction and internal fixation of long-bone fractures in groups with a single dose and 3 doses of prophylactic antibiotic. The secondary aim was to compare the cost-effectiveness of both antibiotic regimens. This is a prospective randomized clinical trial (RCT) to compare the incidence of surgical site infection between the patients allocated randomly into two groups with different antibiotic prophylactic regimens: single dose or 3 doses 8 hourly of 1g ceftriaxone administered intravenously. 200 consecutive patients who underwent open reduction and internal fixation (ORIF) for closed long-bone fractures were enrolled in this study. The rate of postoperative SSI was 4.1% in the single-dose group and 2.2% in the 3-dose group; the overall SSI rate was 3.2%. The primary endpoint of this study, which is the incidence of SSI, showed no significant difference between the single-dose and 3-dose prophylactic antibiotic groups. Furthermore, there was no
Consequence: delay effective treatment in severe sepsis

Mortality increases by 7.6% per hour of delay

Kumar: Crit Care Med 2006; 34:1589–1596)
Aminoglycosides- choice for potential Gram negative sepsis

- Most rapidly bactericidal agent still (concentration-dependent kill)
- Best coverage of Gram negative pathogens based on local patterns of susceptibility
- Australia: safe dosing regimens – maximum 48hrs (3 doses)
Gentamicin questions!

Q3a What weight is used for calculation of gentamicin dosing?
- Actual BWt
- Ideal BWT

Q3b What initial dose of gentamicin is recommended on PNG adult STG?
- 4mg/kg
- 5
- 5-7
- 7mg/kg
- Not sure
Gentamicin questions!

Q3a What weight is used for calculation of gentamicin dosing?

Correct response

<table>
<thead>
<tr>
<th>Ideal body weight</th>
<th>Results (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>27%</td>
</tr>
</tbody>
</table>

Q3b What initial dose of gentamicin is recommended on PNG adult STG?

Correct response

<table>
<thead>
<tr>
<th>5mg/kg</th>
<th>Results (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>27% (60% incl 5-7 response)</td>
</tr>
</tbody>
</table>
Ideal body weight

- Used only for obese patients (>20% over expected)

Ideal Body Weight & Adjusted Body Weight

- Height: Inches
- Weight: Kilograms
- Gender: Male

Calculate
Reset

Background

Ideal body weight

Estimate Ideal body weight in (kg)
Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet.
Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.
Gentamicin: unintended consequences

• Nephrotoxicity – cumulative effect
• Ototoxicity – vestibular function
  – Cumulative dose effect
  – Rare idiosyncratic effect
  – Salicylate may attenuate toxicity

• Cumulative dose effects minimised by:
  – single daily dosing – saturates uptake into sites of potential toxicity
  – Short courses
Gentamicin: safety in practice

Experience with a Once-Daily Aminoglycoside Program Administered to 2,184 Adult Patients
DAVID P. NICOLAU,1,2,3,4 COLLIN D. FREEMAN,1,3† PAUL P. BELLIVEAU,1,3,5 CHARLES H. NIGHTINGALE,3,4 JACK W. ROSS,3 AND RICHARD QUINTILIANI2,5

- 7mg/kg / day; dose interval adjusted in presence of pre-existing renal failure
  - median dose 450mg (R 200 - 925)
  - median length of therapy 3 days (R 1 – 26)
  - median age 46 years (R 13 - 97)
- Clinically apparent ototoxicity:
  - 3 patients (durations of rx before sx: 5 d, 5 weeks!, and third patient had a single dose)
  - Symptoms resolved in patients 1 and 3; patient 2 had some residual changes
- 1.2% developed nephrotoxicity
Q4. What is main mechanism by which *Staphylococcus aureus* becomes resistant to penicillin?

1. Reduced access of drug to the cell (antibiotic can’t penetrate)
2. Betalactamase production (antibiotic is destroyed)
3. Modification of the penicillin binding protein (Antibiotic cannot bind to its target)
4. Increased efflux from the bacterial cell (antibiotic is pumped out so that the intracellular level is too low)
Q4. What is main mechanism by which *Staphylococcus aureus* becomes resistant to penicillin?

- 90% + of methicillin-susceptible strains are resistant to penicillin due to betalactamase
- Clavulanate in Amoxycillin+clavulanate inhibits this
- Flucloxacillin is betalactamase stable

<table>
<thead>
<tr>
<th>Correct response</th>
<th>Results (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betalactamase production</td>
<td>50%</td>
</tr>
</tbody>
</table>
Q5. What is the drug of choice for a methicillin-susceptible *Staphylococcus aureus* bloodstream infection (SAB)?

1. Benpen
2. Flucloxacillin
3. Vancomycin
4. Ceftriaxone
5. Erythromycin
Q5. What is the drug of choice for a methicillin-susceptible *Staphylococcus aureus* bloodstream infection (SAB)?

- Benpen - NO
- Vancomycin – NO – less rapidly acting – inferior outcomes
- Ceftriaxone – NO – technically will work but is too broad spectrum – selects for more resistance
- Eyrthomycin – NO – not suitable for systemic infection

<table>
<thead>
<tr>
<th>Correct response</th>
<th>Results (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flucloxacillin</td>
<td>50%</td>
</tr>
</tbody>
</table>
**Staphylococcus aureus** bloodstream infections

- PMGH 2016: 8 of 11 (78%) events were due to MRSA
- Community and healthcare-associated events occur; risk of undisclosed endocarditis
- Minimum 2 weeks IV therapy required for “uncomplicated” cases - dosing as appropriate for endocarditis
- Vancomycin IV required in PNG!
SAB management

High mortality infection; best practice treatment reduces same: 10 essential steps to consider

See HNELHD.CG.14_20_Management_of_Staphylococcus_aureus_bacteraemia for detailed advice.

What to do if your patient has *Staphylococcus aureus* grown in

1.3 Complicated SAB

Complicated SAB is defined as the presence of ANY of the following features [5]:

- Persistent bacteraemia at 48-72 hours following initiation of appropriate antibiotics.
- Persistent fever for >72 hours following initiation of appropriate antibiotics.
- Bacteraemia where no removable focus of infection is identified (“removable” foci include intravascular lines, drained skin and soft tissue abscesses and simple skin lesions).
- Metastatic focus (e.g. endocarditis, vertebral osteomyelitis, visceral abscesses).
- Intravascular prosthetic material (e.g. prosthetic cardiac valve, pacing wires, pacemaker, implanted defibrillator, prosthetic fistula).

10. Provide verbal & written advice to your patient and their family about the symptoms of relapse and the need for early review if problems occur. The guideline has a patient information card within.

Vancomycin: how to use

- Slow onset of action
- Australian Guidelines Ed 15 - give loading dose of 25-30mg/kg (based on actual body weight)
- Then give 1.5g 12-hrly for GFR>90, lower dosing for patients with renal failure
The clinical spectrum of staphylococcal bacteraemia: a review of 101 Melanesian patients from Papua New Guinea.

John R, Naraqi S, McDonnell G.

- 101 patients with *Staphylococcus aureus* bacteraemia observed during two 2-year periods (1977-1979 and 1985-1987) at PMGH
- 12 to 70 years; 69% male
- Diabetes mellitus (15%) most common predisposing factor.
- 87% had community-acquired infection.
- Sites of infection: soft-tissue infection, pneumonia, arthritis, osteomyelitis, intravenous-site thrombophlebitis, cerebral abscess, endocarditis and cavernous sinus thrombosis
- Soft tissues and lungs most common sites of primary and secondary foci of infection, respectively.
- Penicillin – 1% susceptible; no MRSA detected
- The overall case fatality rate 24%.

Q6: According to the STG, what is the recommended treatment for moderate severity community acquired pneumonia?

1. Benzylpenicillin
2. Ceftriaxone
3. Chloramphenicol
4. Doxycycline
5. Not sure
Q6: According to the STG, what is the recommended treatment for moderate severity community acquired pneumonia?

- Streptococcus pneumoniae remains the most important childhood and adult cause of bacterial pneumonia
- Remains susceptible to penicillin in almost all cases

<table>
<thead>
<tr>
<th>Correct response</th>
<th>Results (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin</td>
<td>62%</td>
</tr>
</tbody>
</table>
12.4.2 Moderate Pneumonia

Symptoms and signs
- Fever, cough, pleuritic chest pain
- Respiratory distress (in-drawing of muscles between ribs, using neck muscles for breathing) OR
- Respiration rate 30-40/min.
- AND no complications

Treatment
Treat as an inpatient. If getting worse after 2 days treatment, treat for severe pneumonia.

- Give
  
  \textit{benzyl-penicillin IV 2 MU (1.2g) every 4-6 hours}

- When improved change to:
  
  \textit{amoxyccillin 500mg t.d.s for 5-10 days}

- Analgesia for chest pain (on page 16)
- Test for malaria (blood slide or Rl)
- Chest physiotherapy/encourage

  Treatment
  - Give:
    
    \textit{chloramphenicol IM or IV 1g (1 whole vial with 4ml sterile water) q.i.d OR}
    
    \textit{benzyl-penicillin IV 2 MU (1.2g) every 4-6 hours AND}
    
    \textit{gentamicin IV 5mg/kg daily OR}
    
    \textit{ceftriaxone IV 1g daily}

  - When the patient improves, has no fever and looks better (usually after 3-5 days) change to:
    
    \textit{chloramphenicol 750mg (3 caps) orally q.i.d for 10 days}
Community acquired pneumonia

- Range of viral, bacterial pathogens

- Non-severe pneumonia – focus on supportive care + penicillin / amoxycillin
  - Non pneumococcal pathogens unlikely to require directed therapy – self limited course
  - Beware possible pertussis in infant

- Severe pneumonia – requires broader spectrum cover for Gram negative pathogens (Klebsiella etc) – penicillin+ gentamicin (short course for gent)
Acute exacerbations of COPD

• Comprehensive viral detection studies indicate that around 70% have had an antecedent viral infection (with one or more of 15 different viruses)
• Most patients are chronically colonised with a range of Haemophilus, Moraxella or Strep. pneumoniae
• Varying degrees of bronchiectasis often present as well if sensitive CT scanning used
• Non-antibiotic management important
  – +/- Physiotherapy
  – +/- Treat bronchospasm
  – self limited illness – await improvement
  – Stop smoking!
Acute exacerbations of COPD (2)

- A minority have obvious pneumonia – beware of overdiagnosis – if pneumonia then exclude TB and treat as pneumonia
- Those without pneumonia need supportive care – oxygen, nebulisers. **Antibiotics play a minor role** – at most, give 3 days of amoxycillin or doxycycline

- Treat chest infection if sputum increases in amount or becomes more green or yellow. Use:
  - amoxycillin 500mg (2x250mg or 1x500mg) t.d.s for 7 days
- If no improvement, give:
  - doxycycline 100mg (1 tab) b.d for 7 days OR
cotrimoxazole (Seprin) 960mg (2 tabs) b.d. for 7 days
Upper respiratory infections

- Adults
  - Overwhelmingly viral causes – avoid antibiotics and manage symptoms (influenza vaccination)
  - Pharyngitis – appearance of throat and tonsils does NOT predict bacterial infection
  - Avoid antibiotics

- Children
  - Peak age incidence for *Streptococcus pyogenes* infection is 5-14 years. Penicillin-V for overt pharyngitis especially in association with cervical LNs.
  - Otitis media – guideline driven – prone to over-diagnosis – antibiotics for infants, those with severe or non-responsive disease; mostly avoid antibiotics
  - Beware pertussis
The *in vivo* susceptibility test

- Scenario 1: patient treated with antibiotic appears to be improving – what are the possible explanations?
  - The antibiotic did it! Take credit...
  - The patient had a self-limited illness and improve despite the treatment that you prescribed
The *in vivo* susceptibility test

- Scenario 1: patient treated with antibiotic appears to be improving – what are the possible explanations?
  - Scenario 2: patient is failing to respond to antibiotic treatment.
    - They have a non-bacterial infection
    - They don’t have an infection!
    - The antibiotic is inactive or the wrong one
    - The infection is due to a multi-resistant organism that is not susceptible to the treatment
    - The illness does not get better that quickly! E.g. typhoid takes a median of 4 days of treatment before temp falls
    - Non compliant patient
Q7: First line treatment for non-severe *Clostridium difficile* diarrhoea

1. Amoxy+clavulanate
2. Clindamycin
3. Vancomycin orally
4. Vancomycin IV
5. Metronidazole oral or IV
Q7: First line treatment for non-severe *Clostridium difficile* diarrhoea

- PNG hospital and community incidence of *C. difficile* infection unknown - Needs to be studied!
- IV vancomycin does not enter the bowel – no use!
- Oral vancomycin is second line – not absorbed and effective
- Treatment is for 7-10 days; relapse not infrequent
- Cross infection risk

<table>
<thead>
<tr>
<th>Correct response</th>
<th>Results (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral/IV metronidazole</td>
<td>50%</td>
</tr>
</tbody>
</table>

Correct response: Oral/IV metronidazole — 50%
Osteomyelitis

• Acute osteomyelitis: symptoms present for < 14 days correlate with acute osteomyelitis histopathologically (i.e. lack of bone necrosis and sequestra). Symptoms > 48 hrs, generally surgery required.

• Chronic osteomyelitis: relapsed or long-standing bone infection that may involve a sinus or a compromised soft-tissue envelope. Pathology—low-grade inflammation, sequestra +/- involucrum (new bone formation adjacent to a sequestrum). Antibiotics AND surgery.
Aetiology - Children haematogenous:
*Staphylococcus aureus, Streptococcus pyogenes*
*Haemophilus influenzae* type B (HIB), *Streptococcus pneumoniae*
*M. Tuberculosis*

Adults haematogenous:
*Staphylococcus aureus, Streptococcus*, *E. coli*

**Treatment**

- Give empiric antibiotics:
  
  *flucloxacillin 1g IV q.i.d for 2-6 weeks (see below)*

- Refer immediately to medical officer

- Intravenous therapy should continue for a minimum of 2 weeks. Thereafter, give:
  
  *flucloxacillin 1g (2 tabs) q.i.d for 4 weeks*

- If there is no improvement with flucloxacillin, consider the possibility of MRSA (methicillin-resistant *Staphylococcus aureus*) and give:
  
  *lincomycin 600mg IV t.d.s for 2 weeks followed by cotrimoxazole 960mg (2 tabs) b.d for 4 weeks*
Management of childhood haematogenous osteomyelitis in a rural Papua New Guinean hospital.
Van Gurp G, Kila R, Hutchinson T.

Abstract
Haematogenous osteomyelitis, especially in its more common chronic stage, is an important cause of morbidity in children in the Southern Highlands Province. Hospital stays are lengthy and the incidence of fractures is high. While awaiting, or in the absence of, culture and sensitivity results, cloxacillin 200 mg/kg/day plus probenecid 40 mg/kg/day is an appropriate first choice antibiotic when it is available. Antibiotic therapy in chronic disease should be limited to the specific settings of associated soft tissue infection; pre- and post-sequestrectomy; and radiological signs of ongoing bone necrosis and systemic signs of active infection. Surgical drainage of subperiosteal pus and possibly the medullary canal is required in all but the very early (less than 48 hours) cases of acute osteomyelitis that sometimes respond to antibiotics alone. Sequestrectomy should be reserved for cases where a sequestrum and adequate involucrum can be seen on X-ray. Effective management of this disease is possible only if ongoing communication exists between hospital-based medical staff and the staff of health centres or subcentres, including the network of aid post orderlies and their supervisors. Since the majority of patients present to facilities other than hospitals, any campaign directed at improving management must involve co-workers in rural areas, namely the health extension officer, nurse and aid post orderly. Only in this way can we hope to achieve earlier appropriate treatment and more systematic long-term follow-up.

PMID: 2856072
<table>
<thead>
<tr>
<th>Condition</th>
<th>Age</th>
<th>Duration of antibiotic therapy (modify according to clinical response)</th>
<th>Total duration (can be completed with oral therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Intravenous [NB1]</td>
<td></td>
</tr>
<tr>
<td>Acute osteomyelitis [NB2]</td>
<td>neonate</td>
<td>4 weeks</td>
<td>4 weeks (all IV)</td>
</tr>
<tr>
<td></td>
<td>child</td>
<td>3 days</td>
<td>minimum 3 weeks</td>
</tr>
<tr>
<td></td>
<td>adult</td>
<td>4 weeks</td>
<td>minimum 6 weeks</td>
</tr>
<tr>
<td>Chronic osteomyelitis [NB2]</td>
<td>child</td>
<td>may not be necessary</td>
<td>minimum 6 weeks</td>
</tr>
<tr>
<td></td>
<td>adult</td>
<td>2 weeks</td>
<td>many months</td>
</tr>
</tbody>
</table>

NB1: If the patient is improving, earlier conversion to oral therapy may be possible, as long as there is an appropriate oral antimicrobial available that is as effective as intravenous therapy (e.g., ciprofloxacin, clindamycin). Conversely, some patients will need a longer duration of intravenous therapy than recommended here. Seek expert advice.
PNG NATIONAL ACTION PLAN ON
ANTIMICROBIAL RESISTANCE

Recommendations under these headings:

1. National coordination mechanisms (governance)
2. Access to, and quality of, essential medicines
3. Surveillance and laboratory capacity
4. Rational use of medicines in humans and animals— a “One Health” approach required – humans, agriculture and animal production
5. Infection prevention and control
6. Research and development
Potential M Med projects!

- Descriptive studies of blood culture isolates, clinical details and antibiograms (where available):
  - *Staph aureus* bloodstream infection (adults, children, neonates)
  - Gram negative bloodstream infections (ditto)
- Antimicrobial prescribing survey – point prevalence- every patient on an a/m – National Antimicrobial Prescribing Survey methods (Oz)
  - Documented reason?
  - When started?
  - Dose and mode of administration
  - In line with STG?
  - In line with documented microbiology for the patient?
- Antimicrobial prescribing and resistance knowledge, attitudes and practice:
  - Surveys of prescribers, students
  - Surveys of community
- Culture surveys of community and hospital patients to document carriage of MROs – MRSA, MRGN
Projects: infection prevention

- Healthcare infection point prevalence survey- hospital wide or ward- WHO methodology
- Surgical wound infection studies- analysis of risk factors, microbiology, use of surgical prophylaxis and potential changes for prevention
- Hand hygiene practice – knowledge, attitudes and practice of healthcare staff – doctors, nurses etc. What are the barriers to uptake/compliance amongst medicos?
- Aseptic practice audits – IV device insertion and management, IV medication preparation, adverse outcomes (local and blood stream infections)
- Bubble humidifiers – microbiological culture survey of the fluid from these devices!
References

- [http://Idmic.net](http://Idmic.net) for access to PNG STG
- [http://aimed.net.au](http://aimed.net.au) for discussions on antibiotic stewardship